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Explaining fatigue in multiple sclerosis: cross-validation of a biopsychosocial model

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Abstract Fatigue is a common and disabling symptom in patients with multiple sclerosis (MS), but its pathogenesis is still poorly understood and consequently evidence-based treatment options are limited. Bol et al. (J Behav Med 33(5):355–363, 2010) suggested a new model, which explains fatigue in MS from a biopsychosocial perspective, including cognitive-behavioral factors. For purposes of generalization to clinical practice, cross-validation of this model in another sample of 218 patients with MS was performed using structural equation modeling. Path analysis indicated a close and adequate global fit (RMSEA = 0.053 and CFI = 0.992). The cross-validated model indicates a significant role for disease severity, depression and a fear-avoidance cycle in explaining MS-related fatigue. Modifiable factors, such as depression and catastrophizing thoughts, propose targets for treatment options. Our findings are in line with recent evidence for the effectiveness of a new generation of cognitive behavioral therapy, including acceptance and mindfulness-based interventions, and provide a theoretical framework for treating fatigue in MS.

Keywords Multiple sclerosis · Fatigue · Catastrophizing · Physical disability · Structural equation modelling · Biopsychosocial model

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Introduction

Multiple sclerosis (MS) is characterized by a chronic inflammation of the central nervous system, which results in demyelination and atrophy, but has an unknown pathogenesis and an unpredictable course. It is one of the most common neurological disorder in young adults (Compston & Coles, 2008) with a prevalence of 0.9 per 1000 (Hirtz et al., 2007). Patients with MS report a variety of physical and neuropsychiatric symptoms, with fatigue being the most frequent and disabling symptom reported: 80–92 % of patients with MS report fatigue, and 40–69 % rate fatigue as their most disabling symptom (Brañas et al., 2000; Giovannoni, 2006; Minden et al., 2006). Fatigue is a major reason for decreased societal participation and is also related to disability and poor quality of life.

Unfortunately, the multifactorial pathogenesis of fatigue in MS is not completely understood, and evidence-based treatment options remain scarce (Asano et al., 2014; Bol et al., 2009; Kos et al., 2008; Pucci et al., 2007). Bol et al. (2010) examined its multifactorial pathogenesis by fitting a biomedical and a cognitive behavioral model in a sample of 262 patients with MS using structural equation modelling (SEM). Results showed that both models poorly explained fatigue in MS, and based on previous research and the results of their SEM analyses, they formulated a new model. This final model was an integration of the first two models, including both biomedical and cognitive-behavioral factors, and can be considered as the fatigue equivalent of the fear-avoidance model of chronic musculoskeletal pain (Crombez et al., 2012; Vlaeyen et al., 1995). In this integrated model, catastrophizing about fatigue has a central role: being fueled by depression, it mediated the relationship between fatigue and fatigue related fear and avoidance behavior (Bol et al., 2010).

Catastrophizing about fatigue is defined as a fearful interpretation of the meaning of fatigue by exaggerated negative thinking, magnification of symptoms, and helplessness (e.g. 'fatigue is terrible and I think it can never improve' or 'when I feel tired, there is nothing I can do to decrease its intensity') (Lukkahatai & Saligan, 2013). If fatigue is erroneously interpreted as a sign of pathology over which one has little or no control, this could gradually extend to a fear and avoidance of physical activities and subsequently decreased physical abilities. According to the fear-avoidance model, this would then lead to an increase in fatigue concluding its cyclic pattern. Lukkahatai and Saligan (2013) showed in their systematic review a consistent strong positive correlation between catastrophizing and fatigue severity in several clinical conditions that share fatigue as one of their core symptoms, such as multiple sclerosis, chronic fatigue syndrome, fibromyalgia and cancer.

Besides the role of catastrophizing and fear-avoidance behavior, previous research has shown a significant association between depression and fatigue in patients with MS, independent of physical disability (Bakshi et al., 2000). With regard to the direction of influence, a longitudinal study of Patrick et al. (2009), including 2768 patients with MS, showed that depression was one of the most important predictors of fatigue at 1-year follow-up. With regard to disease severity, Hadjimichael et al. (2008) showed a significant positive correlation between disease severity and fatigue in patients with MS, explaining that more physical disability and neurological impairment are associated with higher levels of fatigue.

This biopsychosocial model of Bol et al. (2010) integrates these individual observations in a single model of fatigue in MS, however cross-validation is necessary to make a valid generalization and application to everyday clinical practice possible. In the present study, we hypothesize that the associations between fatigue, depression, catastrophizing and disease severity described by the biopsychosocial model will explain fatigue in another large group of MS patients. This cross-validation is important for the understanding of the origin and perpetuating of fatigue in patients with MS and will provide a theoretical framework for treating fatigue in patients with MS.

Methods

Participants

Participants were recruited from hospital databases of the department of Neurology of the Zuyderland Medical Center in Sittard-Geleen, the Netherlands. A total of 621 Dutch-speaking patients with clinically definite MS according to McDonald criteria (Polman et al., 2005), aged between 18 and 65 years, were eligible for inclusion. Their treating neurologist sent the initial letters to secure confidentiality. A total of 403 patients were interested in participating and responded (65 % response rate). These patients were sent an information letter, an informed consent and questionnaires. A total of 312 participants returned the forms (77 % response rate). Questionnaires were filled in between May 2011 and September 2011. Participants who previously participated in the study of Bol et al. (2010) ($N = 86$) were excluded. Informed consent was obtained from all participants included in the study. Patients did not receive any financial compensation for their participation.

Measures

Basic demographic information

Age, gender, level of education, employment status, marital status and use of psychopharmacological drugs were obtained by a demographic inventory filled in by the patients. The level of education was based on the highest completed level of education and divided into three categories: primary school (low level of education); junior vocational training (middle level of education); senior vocational training or academic training (high level of education). Medical data, such as disease duration, disease course, MS subtype and disease severity were collected from the hospital databases.

Disease severity

Disease severity was assessed with the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). This scale comprises the evaluation of 8 functioning systems (pyramidal, cerebellar, brainstem, mental, bowel and bladder, visual-optic, sensory and other). The EDSS score, based on the evaluation of an experienced neurologist, ranges from 0 to 10, where 0 indicates a normal neurological examination and 10 indicates death due to MS. Recent EDSS scores (<3 months) were extracted from the hospital database.

Physical disability

Physical disability was assessed with the physical dimension of the SF-36, a Dutch translation of the Short Form Health Survey developed and validated by Aaronson et al. (1998). Bol et al. (2010) showed a high reliability of this measure in patients with MS. It consists out of four subscales; physical functioning, role limitations due to physical health problems, bodily pain, and general health. Each

standardized subscore of the physical dimension ranges from 0 to 100, where a total score of 400 resembles optimal physical health and no physical disability.

Fear avoidance

Fear avoidance was assessed with the fatigue version of the Tampa Scale for Kinesiophobia (TSK-F) (Silver et al., 2002), which is an adjusted version of the TSK for chronic pain (Miller et al., 1991; Vlaeyen et al., 1995). Silver et al. (2002) replaced in all 17 items the word 'pain' by the word 'fatigue' to make the questionnaire suitable for investigation of fatigue-related fear and avoidance behavior. The score ranges from 17 to 68, where a higher score indicates a higher level of fear-avoidance behavior. This instrument is found to be valid (Silver et al., 2002) and reliable in patients with MS (Bol et al., 2010; Silver et al., 2002).

Catastrophizing

Catastrophizing about fatigue was assessed with the Fatigue Catastrophizing Scale (FCS), which is an adapted version of the Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995). Psychometric properties of the PCS are adequate (Osman et al., 2000). The PCS consists out of 13 items measuring the self-reported frequency of catastrophizing thoughts about experienced pain. As with the TSK adaptation, Bol et al. (2010) adapted all the PCS items by replacing the word 'pain' by the word 'fatigue'. Scoring alternatives ranged from 'strongly disagree' to 'strongly agree'. As in the study of Bol et al. (2010), three MS-related items were added ('When I am tired, this is a signal there is something wrong in my brain', 'When I am tired, this is a warning for physical decline', 'When I am tired, this is a sign that my MS is getting worse'). In total 16 items were administered and the score ranges from 0 to 64 with higher scores indicating higher intensity of catastrophizing. Bol et al. (2010) showed a high reliability of this measure in patients with MS. In the current sample the reliability was excellent ($\alpha = 0.94$).

Fatigue

Fatigue was assessed with the Abbreviated Fatigue Questionnaire (AFQ), a valid and reliable instrument (Alberts et al., 1997). Administration to patients with MS also revealed its reliability (Bol et al., 2010). This questionnaire is a selection of four items of the Checklist Individual Strength (CIS-20) developed by Vercoulen et al. (1999). Items are rated on a 7-point Likert scale with scoring alternatives ranging from 'Yes, that is true' to 'No, that is not true'. The final score ranges from 4 till 28, with higher scores indicating a higher severity of physical fatigue.

Depression

Depression was assessed with the subscale depression of the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983), a valid and reliable screening instrument for patients with MS (Honarmand & Feinstein, 2009). The total score ranges from 0 to 21 with a higher score indicating a higher intensity of depression. Honarmand and Feinstein (2009) showed that patients with MS with a score of 8 or higher are likely depressed.

Statistical analyses

Data analyses were performed using SPSS 22.0.0.0 for Windows (SPSS Inc., Chicago, IL). If less than 25 % of the items of questionnaires, or more than 50 % if a questionnaire consisted of four items, were missing, missing values were imputed by the mean of the remaining non-missing items of the scale (27 values across 24 participants). Descriptive statistics were used to describe the sample. No variable was significantly skewed (skewness <-1 or >1) nor were there any significant outliers (all cases were within 1.5 interquartile ranges from the upper or lower quartile). Cronbach's alpha was used to test reliability of all questionnaires. Relations between all variables were analyzed by Pearson-correlations. An alpha level of .05 was used for all statistical tests.

Cross-validation was analyzed with structural equation modeling in Mplus 7 (Muthén & Muthén, 1998–2012). The biopsychosocial model of Bol et al. (2010) was specified in a path analysis using manifest variables only (no measurement model). Error terms were assumed to be uncorrelated and left free. The Root Mean Square Error of Approximation (RMSEA) was used as a global fit index, because parsimony and sample size are taken into account. RMSEA represents the lack of fit in comparison with a perfect fit and should therefore be low. RMSEA values up to 0.05 indicate a close fit, values between 0.05 and 0.08 indicate an acceptable fit, values between 0.08 and 0.10 indicate a mediocre fit, and those greater than 0.10 indicate a poor fit. Furthermore, the comparative fit index (CFI) was used, because it represents the relative improvement of the model in comparison with a baseline model, usually a model in which all observed variables are uncorrelated. Values larger than 0.95 indicate a good fit and values between 0.90 and 0.95 indicate an acceptable fit. Furthermore, the Chi square test of model fit, Standardized Root Mean Square Residual (SRMR) and Tucker–Lewis Index (TLI) were also reviewed as fit indexes. A non-significant Chi square test of model fit indicates a

good fit. SRMR values smaller than .08 indicate an acceptable fit, whereas values smaller than 0.05 indicate a good fit. TLI values higher than .90 are acceptable and values higher than .95 represent a good fit. To control for possible normality assumption violation, a robust maximum likelihood estimator for standard errors, also known as the 'Huber Sandwich Estimator', was used (Huber, 1967). Modification indices were inspected to consider further fine-tuning of the model to the data-at-hand in an exploratory fashion. Finally, direct and total effects of the significant variables were calculated.

Results

Patient sample

A total of two participants were excluded due to too many missing values (>25 % of items of questionnaires missing). Finally, six participants were excluded due to a missing value in the single exogenous variable, EDSS, which was necessary for proper structural equation modeling (SEM) analysis. This resulted in a final sample of 218 outpatients (53 men, 165 women) with an average age of 48.0 years ($SD = 10.5$, range 19–65). Most of them had a relapsing remitting disease course ($n = 153$), while 43 patients had a secondary progressive disease course and 21 patients had a primary progressive disease course (1 missing value). The mean disease duration was 8.8 years ($SD = 7.5$, range 0–30 years) with an average EDSS score of 3.6 ($SD = 1.9$, range 0.5–8.0), which resembles a moderate disease severity. Around 24 % of the sample showed high levels of catastrophizing, using the cutoff score of 30 as suggested by Sullivan et al. (1995) for patients with pain. Around 34 % of the sample showed high levels of fear avoidance, using the cutoff score of 37 as suggested by Vlaeyen et al. (1995) for patients with pain. See Table 1 for a summary of all patient characteristics.

Table 1 Patient characteristics (n = 218)

Variable	Value
Gender % female (*n*)	76 (*165*)
Age in years [mean (SD)]	48.0 (10.5) range 19.6–65.6
Disease duration in years [mean (SD)]	8.8 (7.5) range 0.1–30.2
Disease course	
Relapsing remitting (%)	71
Secondary progressive (%)	20
Primary progressive (%)	9
Use of disease modifying drugs (% yes, % no)	61/39
Use of psychopharmaca (% yes, % no)	25/75
Level of education (% low, % middle, % high)	24/37/39
Marital status (% partner, % no partner)	82/28
Employment status (% working, % not working)	32/68

Reliability and correlations

Table 2 resembles means, standard deviations, ranges, reliability indexes (Cronbach's alphas) for all measures and their intercorrelations (Pearson). All questionnaires had a satisfactory internal consistency (range 0.69–0.94). All intercorrelations were statistically significant ($p < 0.01$) with the strongest correlation between depression and physical disability. Higher levels of depression were associated with lower levels of physical ability ($r = -0.58$, $p < 0.001$). The weakest correlation was found between disease severity and catastrophizing about fatigue ($r = 0.21$, $p < 0.01$).

Structural equation modeling analyses

Figure 1 shows the results of the path analysis of the new model proposed by Bol et al. (2010). The RMSEA value was 0.053 (90 % CI 0.000–0.112), which indicates an acceptable fit. The SRMR, CFI and TLI value were respectively 0.023, 0.992 and 0.979, indicating a good fit. The Chi square test of model fit was non-significant ($p = 0.138$) also indicating a good fit. Furthermore, all hypothesized relationships were statistically significant. The total explained variance of fatigue measured with the AFQ was 44 %. All variables provided a significant contribution to this explained variance. Both depression ($\beta = .27$) and physical disability ($\beta = -.45$) were directly associated with fatigue. There were no modification indexes given, suggesting that no alternative specification of relationships between the variables were identified which could improve the model. We added a relationship from disease severity to depression, due to its significance in the second model postulated by Bol et al. (2010), but this worsened the global fit of our model and was subsequently removed. Moreover, we ran an additional post hoc analysis to study the variance in fatigue explained by the fear avoidance cycle. For this, we omitted the paths to and from depression and disease severity (see Fig. 1) from the model. This showed that physical disability, fear-avoidance, catastrophizing and their underlying associations explain 39 % of the variance in fatigue, compared with

Table 2 Means, standard deviations (SD), ranges, Cronbach's alphas (α) and Pearson-correlations of all measures

	Mean (SD)	Range	α	2	3	4	5	6
1. Disease severity (EDSS)	3.6 (1.9)	0.5–8	–	.23**	.21*	.22**	.29**	−.48**
2. Fatigue (AFQ)	19.7 (6.8)	4–28	0.90	–	.55**	.34**	.54**	−.63**
3. Catastrophizing about fatigue (FCS)	19.9 (14.1)	0–56	0.94	–	–	.58**	.57**	−.55**
4. Fatigue-related fear and avoidance (TSK-F)	34.3 (8.3)	20–68	0.73	–	–	–	.41**	−.42**
5. Depression (HADS-D)	6.0 (4.0)	0–17	0.82	–	–	–	–	−.58**
6. Physical disability (SF-physical)	208.5 (92.1)	25–400	0.69	–	–	–	–	–

EDSS Expanded Disability Status Scale, *AFQ* Abbreviated Fatigue Questionnaire, *FCS* Fatigue Catastrophizing Scale, *TSK-F* Fatigue Version of the Tampa Scale for Kinesiophobia, *HADS-D* depression subscale of the Hospital Anxiety and Depression Scale, *SF-physical* Physical scale of the Short Form Health Survey

* $p < 0.01$; ** $p < 0.001$

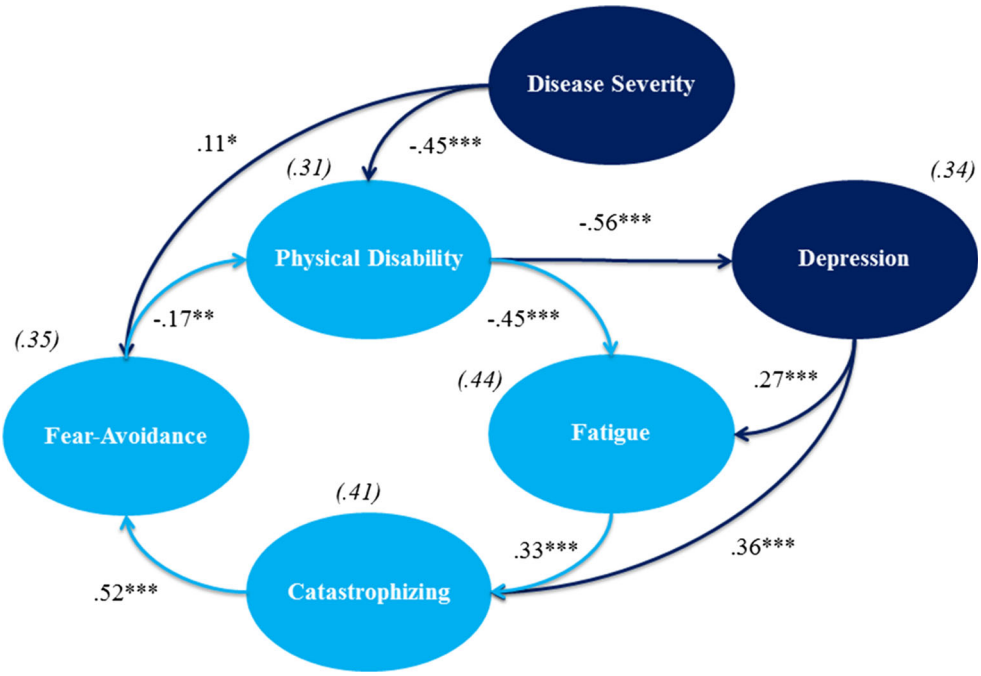

Fig. 1 Path analysis of the biopsychosocial model of fatigue in multiple sclerosis (n = 218). *Note* Values shown are standardized regression coefficients and based on cross-sectional data. *Light blue* variables and its relationships represent the fear-avoidance cycle within the model. Explained variances are provided in parentheses. Please note that the scale of physical disability is inverted. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ (Color figure online)

44 % of the total model. See Table 3 for an overview of the standardized direct, indirect and total effects on fatigue.

Discussion

Due to the high prevalence of fatigue in patients with MS and its disabling impact on everyday activities and quality of life, understanding its pathogenesis and identifying its modifiable contributing factors are crucial. Bol et al. (2010) showed that neither a biomedical nor a cognitive-behavioral model explained fatigue in 262 patients with MS, but suggested a new biopsychosocial model integrating elements of the previously tested models, i.e. disease severity, depression and fear-avoidance cycle. To generalize and apply this model to everyday clinical practice, cross-validation of this integrated model in another sample was needed. We hypothesized that the biopsychosocial model of Bol et al. (2010) can explain fatigue in MS in another large sample.

Table 3 Standardized direct, indirect and total effects on fatigue

Variable	Direct	Indirect	Total
Fear-avoidance (TSK-F)	0.000	0.103**	0.103**
Physical disability (SF-physical)	−0.447***	−0.173***	−0.620***
Depression (HADS-D)	0.274***	0.024*	0.298***
Disease severity (EDSS)	0.000	0.288***	0.288***
Catastrophizing (FCS)	0.000	0.054*	0.054*

TSK-F Fatigue Version of the Tampa Scale for Kinesiophobia, *SF-physical* Physical scale of the Short Form Health Survey, *HADS-D* depression subscale of the Hospital Anxiety and Depression Scale, *EDSS* Expanded Disability Status Scale, *FCS* Fatigue Catastrophizing Scale

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

The SEM analyses presented in this study, explaining fatigue in a new sample of 218 patients with MS, showed good support of the biopsychosocial model of Bol et al. (2010). Catastrophizing, depression, physical disability, disease severity and fear avoidance all contribute significantly to fatigue, either directly or indirectly. Comparing the results to that of the original publication, the global fit indices RMSEA and CFI even slightly improved respectively from 0.085 towards 0.053 and from 0.983 towards 0.992. This implies an increase in fit from mediocre to acceptable (RMSEA) or even good (CFI).

The biopsychosocial model indicates a significant role for disease severity, depression and an adapted fear avoidance model in explaining MS-related fatigue. This integrated model partly overlaps with a recently formulated model by Wu et al. (2015) explaining post-stroke fatigue. They suggest also an integration of biological and psychological variables, including depressive symptoms, coping and behavioral factors. Also in stroke patients, an intervention including CBT elements showed a long term reduction in fatigue (Zedlitz et al., 2012). Moreover, Zedlitz et al. (2012) stated that the addition of graded activity to the cognitive elements, which focuses on improvement of physical disability, resulted in a longer endurance of the fatigue reducing effects.

Translating the biopsychosocial model of Bol et al. (2010) to clinical practice in MS, the model indicates several modifiable factors, such as the fatigue-enhancing cycle of fear avoidance and depression, which form important targets for interventions. Diagnosing and treating depression could be a first step to treat MS related fatigue. Depression is with a life-time prevalence of approximately 50 % very prevalent in MS and probably underdiagnosed and untreated (Feinstein, 2011; Maier et al., 2015). When depression is treated, for instance with cognitive behavioral therapy (CBT) (Hind et al., 2014), it is likely that fatigue is also reduced. Next, CBT focusing on changing catastrophizing thoughts about fatigue could help fatigued MS patients (Knoop et al., 2011; Moss-Morris et al., 2012; van Kessel et al., 2008). Knoop et al. (2011) concluded that changes in thoughts about fatigue play a crucial role in CBT for fatigue in MS. Hoogerwerf et al. (submitted) showed that also the third generation CBT, Mindfulness Based Cognitive Therapy (MBCT) is an effective intervention for severely fatigued MS patients. Patients were not only less fatigued after MBCT, but also less depressed and less catastrophizing about fatigue. This suggests that catastrophizing can be reduced not only by altering the content of thoughts such as in regular CBT, but even by disengaging from the maladaptive thoughts about fatigue.

There are several limitations to this study, which should be taken into account when interpreting the results and could be addressed in future studies. First of all, the design is cross-sectional making it impossible to draw firm conclusions about causality and temporal relations in the disease process. More prospective and longitudinal studies are needed to confirm the proposed causal relationships. Secondly, postal questionnaires were used which made us unable to compare responders with non-responders. The response rate was favorable (77 %), but lower in comparison with Bol et al. (2010) (93 % response rate). A possible explanation could be related to the fact that more questionnaires were included which demanded more time and energy of the participants. As a result, we cannot exclude the possibility of a selection bias. Thirdly, all data were self-reported and are therefore sensitive to retrospective bias and response styles. Fourthly, our main outcome measure, the AFQ, is a questionnaire consisting out of four items. Despite its sufficient validity and reliability, Horemans et al. (2004) argued that the AFQ lacks precision at the individual patient level. Future studies should include fatigue questionnaires which are validated in MS patients, such as the Fatigue Severity Scale or the Modified Fatigue Impact Scale (Rietberg et al., 2010). Finally, other factors, some even modifiable, such as sleep disorders, cognitive impairments and maladaptive coping styles, were not assessed and therefore lacking in the biopsychosocial model. Their inclusion could increase the explained variance of the model due to their previously established influences on fatigue in MS (Rabinowitz & Arnett, 2009; Strober & Arnett, 2005; Ukueberuwa & Arnett, 2014). Furthermore, the overall anxiety level and other distorted

cognitive thinking habits besides catastrophizing, in which elements of rumination, magnification and helplessness are embedded (Sullivan et al., 1995), could possibly be another useful addition for future studies due its modifiable character and insight in effective therapeutic elements.

Despite these limitations, this cross-validation of the biopsychosocial model of Bol et al. (2010) forms an important next step in explaining MS-related fatigue and highlights a promising role for CBT. The integrated model supports the clinical practice guidelines that both biological and psychological factors should be taken into account during the clinical assessment and treatment of fatigue in MS (CBO, 2013; Van Kessel & Moss-Morris, 2006). It is expected that development and evaluation of targeted psychological interventions will help improving the biopsychosocial model of MS related fatigue.

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Compliance with ethical standards

Conflict of interest Melloney L. M. Wijenberg, Sven Z. Stapert, Sebastian Köhler and Yvonne Bol declare that they do not have any conflict of interest.

Human and animal rights and Informed consent All procedures were approved by and in accordance with the ethical standard of the medical ethics committee of Zuyderland Medical Center and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all patients for being included in the study.

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